power to discover common variants associated with AD-PID.

Flashfm-ivis: interactive visualisation for fine-mapping of multiple quantitative traits

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Joint fine-mapping that leverages information between quantitative traits could improve accuracy and resolution over single-trait fine-mapping. Using GWAS summary statistics, flashfm (FLexible And SHared information Fine-Mapping) fine-maps signals for multiple traits. We introduce the web tool (and R package) flashfm-ivis, which provides a suite of interactive visualisation plots to identify and view likely causal genetic variants that are either shared or distinct between multiple quantitative traits. It also compares results between single- and multi-trait fine-mapping. Flashfm-ivis also works for single-trait fine-mapping results from FINEMAP as a general-purpose tool for interactive visualisations. Flashfm is in a Bayesian framework, where prior model probabilities are formulated to favour model combinations that share causal variants to capitalise on information between traits. Flashfm-ivis interactively visualises the connections among these SNPs in different traits and methods by: (1) comparing inter-linked and finemap-integrated Manhattan plots; (2) displaying and downloading user-selected SNPs from different combined credible sets in Venn diagrams and Radar plots; (3) connecting SNPs into groups (then groups into networks) based on user-controlled (marginal) posterior probability in dynamic networks and Sankey flowcharts.
While flashfm is computationally efficient and can easily be deployed across publicly available summary statistics for signals in up to six traits, flashfm-ivis offers users flexible ways to compare both flashfm and FINEMAP outputs and explore the insights of joint fine-mapping further. To increase reusability, flashfm-ivis provides both a web-based interface that can be used immediately online without specific programming experience and a standalone R package.

Genetic architecture of longitudinal obesity trajectories in primary care electronic health records

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Genome-wide association studies (GWASs) for obesity (body mass index (BMI)) have identified hundreds of associated loci. However, cross-sectional outcomes do not capture the biology of weight change over adult lifespan.
Here, we integrate UK Biobank-linked genotyping with primary care electronic health records (GP-EHRs) in ~250,000 individuals with >2.8 million observations of BMI and weight to discover genetic associations with obesity trajectories. We model adiposity change with mixed effects models with random slopes for time and, crucially, capture non-linear effects of time with natural cubic splines. We perform GWAS on components of obesity trajectories, including intercept, slope, and cluster identity defined by mixture model clustering of spline coefficients. Three independent variants are significantly associated with weight change per year adjusted for baseline weight: rs814573 (β=0.058 per SD increase in weight per year, P=2.8E-39), rs811041 (β=0.022, P=3.1E-09), and rs1596181 (β=-0.018, P=4.5E-08), each of which
reside in known cholesterol loci. 98 independent variants are associated with modelled intercepts of BMI, 6 of which represent novel loci for BMI or other obesity-related phenotypes. Incorporating longitudinal information offers increased power to detect associations. We observe a 14% boost in effective sample size over that expected from cross- sectional outcomes alone. Further, by accounting for longitudinal information, we are able to classify individuals by disease risk, and characterise genetic loci associated with non-linear obesity trajectories.
This is, to our knowledge, the largest study of its kind, demonstrating the potential of leveraging